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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,824	06/25/2001	Eric Perrier	11123.24US01	9749

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EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,824	PERRIER ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70,72-78,82-86,91,96 and 98-102* is/are pending in the application.

4a) Of the above claim(s) *101 and 102* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70,72[redacted]-78,82-86,[redacted],96 and 98-100* is/are rejected.

7)☒ Claim(s) [redacted] *91* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Election/Restrictions

Newly submitted claims 101 and 102 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claims are directed to therapeutic compositions for inhibiting LPL. The restriction set forth in the Office action of 9/26/02 restricted the screening method, LPL inhibitors and methods of therapy of disorders related to fatty acid deposits as distinct inventions. Applicant elected, without traverse, the screening method in the reply filed 10/25/02.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 101 and 102 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

Claims 73-75 are objected to because it is improperly amended. The amended claim is missing words that have been supposedly be deleted from the claim. All words that are intended to be deleted in an amendment claim must have a line drawn them. Claims 74 and 75 depend from claim 73. Appropriate correction is required.

Applicant's arguments with respect to claims 70, 72-78, 82-86, 91, 96 and 98-102 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 70, 72, 76, 78, 82, 84, 85, 86, 96, and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comai et al. (US 4,218,443; "Comai") in view of Muller et al. (US 6,783,949; Muller"; new reference), the NEFA-C kit from Wako and Wang et al. (J. Lipid Res. (1993) 34: 2091; "Wang"; new reference).

Comai discloses an *in vitro* cell-free method for determining if ionophores are inhibitors of LPL and suitable for anti-obesity and hypotriglyeridemic agents in warm blooded agents. Comai discloses that acetone powders of rat epididyml adipose tissue were obtained from homogenized adipose tissue. After filtration, the extract was washed with acetone and ethyl ether and then dried under vacuum (col. 19, lines 47-65). "The lipoprotein lipase was extracted from the acetone powder into 0.05 M NH_4OH-NH_4Cl buffer" (lines 64-65). Applicant is particularly directed to col. 19, lines 51-52 which refer to their preparation as the "separation of molecular species of lipoprotein lipase from adipose tissue." This disclosure establishes that the LPL used for the assay is separated from cells and cell lysates since the LPL was transferred from the homogenate into the NH_4OH-NH_4Cl buffer.

The activity of the LPL was determined by combing the LPL with substrate comprising ^{14}C-labelled glycerol trioleate (triolein, as in instant claims 78, 82, 96 and 98), lysophosphatidylcholine, bovine serum albumin (as in instant claim 76) and fasted rat serum. The liberated ^{14}C-labelled free fatty acids were extracted into a carbonate buffer and the radioactivity was quantified. The ionophores were added as solutions in water or DMSO to the assay and LPL inhibition was measured. Thus, LPL was measured in the presence and absence of the inhibitor, as in instant claim 72. The ionophore inhibitors were also tested *in vivo* to determine their ability to inhibit lipolysis and effect weight loss (col. 20, lines 3-48). Thus, Comai establishes that an *in vitro* cell-free or cell-free lysate is used to assay inhibitors that

inhibit LPL for the purpose of determining compounds suitable for therapeutic compositions that limit the uptake of fatty acids by adipocytes *in vivo* in order to reduce obesity and hyperlipidemia.

Comai does not teach that the release of fatty acids is enzymatic or the addition of a colipase.

Muller discloses that the determination of lipolytic activity is important because they control the amount of free fatty acids in cells and are responsible for the pathogenesis of a number of diseases. Muller discloses that the activity of lipases *in vivo* is hard to assess. Muller discloses that lipolytic activity can be determined *in vitro* by radiometric, titrimetic, enzymatic or fluorometric/photometric methods. Radiometric assays are the most sensitive but they are expensive and require the disposal of radioactive waste (col. 1, lines 52-68). Thus, Muller establishes that the *in vitro* measurement of lipolytic enzymes, including LPL, is acceptable for determining inhibitors for therapeutic purposes. Muller indicates that radiometric, titrimetic, enzymatic or fluorometric/photometric methods for determining lipolytic actiivty are well known by the ordinary artisan and are equivalent in their respective abilities to measure the release of free fatty acids from lipolysis.

The NEFA-C kit from Wako is a commercial reagent kit that employs acyl-CoA synthetase, acyl CoA oxidase and peroxidase to react with free fatty acids to produce a change in OD at 550 nm in order to determine the concentration of non-esterified fatty acids in a sample.

Wang et al. disclose that optimal LPL assay conditions for the hydrolysis of long chain triacylglycerols requires the combination of bovine serum albumin with apoC-II colipase because they act synergistically for the preferential activation of long chain substrates. A long chain substrate includes C-18 (triolein) (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ apoC-II colipase in the LPL assay and to employ an enzymatic method instead of a radiometric method to determine the amount of free fatty acids liberated in the LPL assay of Comai. The ordinary artisan would have been motivated to use an enzymatic assay to determine LPL activity because radiometric assays are expensive and require the disposal of radioactive waste. The enzymatic method

does not have these inconveniences and Muller established that the methods are equivalent in achieving the measurement of free fatty acids in lipolysis assay. The ordinary artisan would have had a reasonable expectation that the free fatty acids liberated by LPL in the assay of Comai could be determined by the NEFA-C kit because the kit is in commercial use and employs a chain of enzyme reactions that are known to produce a reliable change in OD at 550.

The ordinary artisan would have been motivated to add apoC-II colipase to the assay mixture because it acts synergistically with BSA, which is present in Comai's assay mixture, to optimize assay conditions for long chain triglycerides such as triolein which is employed in the Comai assay. The ordinary artisan would have had a reasonable expectation that the addition of apoC-II colipase to the reaction mixture of Comai would be successful because Wang demonstrated that the combination of apoC-II colipase and BSA causes a shift of LPL longer chain triglyceride substrates.

Thus, Comai in view of Muller and the NEFA-C kit clearly teach that the ordinary artisan would have known that one could identify inhibitors of LPL intended for therapy to limit the uptake of fatty acids by adipocytes by an *in vitro* cell-free or cell-free lysate assay. However, the combined disclosures do not teach specifically teach using an *in vitro* cell-free or cell-free lysate to assay for LPL inhibitors that can be used in a topical composition or for stimulating microcirculation. These limitations have not been given patentable weight because the although the recitation occurs in the preamble and the body of the claims, the limitation only recites the purpose of a process and the actual steps of the claims do not depend on either phrase for completeness but, instead, the process steps are able to stand alone. Even if one were to give the phrases patentable weight, the combined disclosures teach the claimed assay. Thus, any compound identified by the assay is suitable for a topical composition or to stimulate microcirculation because the identified compound can inhibit LPL and thus cause the reduction in size of adipocytes which is the desired therapeutic effect. "The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the

manufacturing process steps would be expected to impart distinctive structural characteristics to the final product." See, e.g., In re Garnero, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979).

Claims 70, 72, 76-78, 82-86, 96, and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comai et al. (US 4,218,443; "Comai") in view of Muller et al. (US 6,783,949; Muller"; new reference), the NEFA-C kit from Wako and Wang et al. (J. Lipid Res. (1993) 34: 2091; "Wang"; new reference), as applied to claims 70, 72, 76, 78, 82, 85, 86, 96, and 98-100, in further view of Vanio et al. (1982; "Vanio").

The combined disclosures by Comai, Muller, the NEFA-C kit and Wang (1993) are discussed *supra.*

The combined disclosures do not disclose the use of a colipase that is apoC-II colipase from a human source, the use of LPL from a bovine milk source or the additional steps of instant claim 83.

Vanio discloses that LPL requires apoC-II colipase for maximal activity. ApoC-II is a protein component of the surface film of both chylomicrons and VLDL in the *in vivo* substrates of LPL (p. 387-388. bridging paragraph). Vanio teaches an assay for LPL activity wherein the source of the purified LPL was bovine milk while the apoC-II colipase was human VDL. The cell-free assay was carried out by reacting the radio-labelled triolein substrate in a mixture containing BSA and heparin with the LPL (p. 387, left column). Thus, Vanio establishes that apoC-II colipase has two *in vivo* functions: to activate LPL *in vivo* as well as serving as part of the complex comprising the *in vivo* substrate.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ LPL isolated from bovine milk and human apoC-II in the assay disclosed by the combined references as well as adding the steps of instant claim 83. The ordinary artisan would have been motivated to use LPL isolated from bovine milk in the assay taught by the combined references because it appears to be interchangeable with human LPL. The ordinary artisan would have come to this conclusion because Vanio employs bovine milk LPL with apoC-II colipase from a human source. Given that it was

known at the time the colipase was an activator of LPL, the employment of an enzyme and colipase from different species suggests that the sources of the LPL and colipase are not critical to the assay.

The ordinary artisan would have been motivated to incubate apoC-II colipase with LPL and the substrate prior to combining the LPL and the substrate because apoC-II colipase is known to interact with LPL and the substrate *in vivo*. The ordinary artisan would have realized from Vanio the importance of mimicking the *in vivo* lipolytic conditions. The ordinary artisan would have had a reasonable expectation that the apoC-II colipase could be incubated with the LPL and substrate before the combination of said LPL and substrate because the association of LPL and the substrate occurs *in vivo*.

Claims 70, 72-78, 82-86, 96, and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comai et al. (US 4,218,443; "Comai") in view of Muller et al. (US 6,783,949; Muller"; new reference), the NEFA-C kit from Wako, Wang et al. (J. Lipid Res. (1993; new reference) 34: 2091; "Wang"), and Vanio et al. (1982; "Vanio"), as applied to claims 70, 72, 76, 78, 82, 85, 86, 96, and 98-100, in further view of Kobayashi (US 3,875,007).

The combined disclosures by Comai, Muller, the NEFA-C kit , Wang (1993) and Vanio (1993) are discussed *supra*.

The combined disclosures do not disclose that the activity of an inhibitor is compared to the effect of a compound known to inhibit LPL activity, wherein the compound is protamine sulfate, protamine or sodium pyrophosphate.

Kobayashi discloses that the lipolytic activity of a substance designated as GA-56 was established, in part, by comparing the activity of known inhibitors of LPL on its activity. The known LPL inhibitors included protamine sulfate. None of the known LPL inhibitors had any effect on the lipolytic activity of GA-56. Kobayashi concluded that GA-56 was not a like known LPL's (Table I).

It would have been obvious to one of ordinary skill in the art to compare the activity of an experimental inhibitor with that of a known LPL inhibitor. The ordinary artisan would have been

motivated to do so because the comparison provides information regarding the ability to inhibit LPL activity compared to a known quantity.

Claim 91 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan Hanley
Patent Examiner
1651

Irene Marx

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PRIMARY EXAMINER